Optimal cancer chronotherapeutics schedules using a Systems Biology approach

Chronotherapeutics of Seliciclib

Dr. Christophe Chassagnole, COO

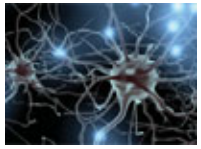
About Physiomics plc

- **Business**
  - Founded 2001, Oxford (UK) based, listed on the LSE (AIM) 2004
  - We use computer modelling to understand and predict optimal cancer therapy.
  - We accelerate the discovery process and reduce development risk.
- **Focus**
  - Cancer
  - Models to simulate drug mechanism of action.
  - Combination therapy and cell populations (SystemCell® Technology).
- **Collaborations:**
  - Eli Lilly
  - Cyclacel Pharmaceuticals
  - ValiRx - Cronos Therapeutics
  - Bayer Technology Services
  - TEMPO (FP6 – EU LifeSciHealth project)
  - Institute of Life Science, Swansea University (HPC)

Bayer Technology Services

Valirx Bioscience Innovation

CYCLACEL



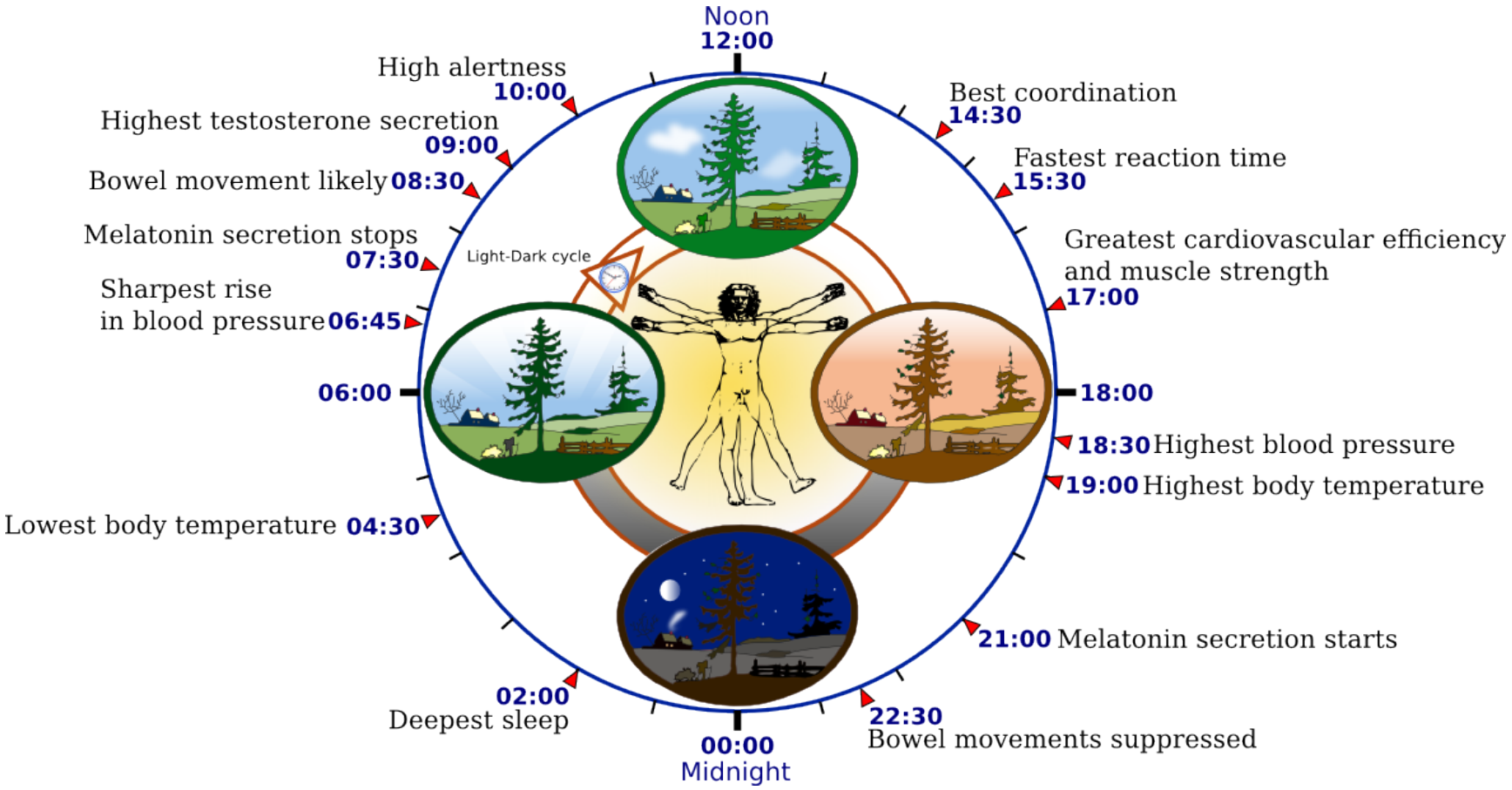
TEMPO

Chronotherapy for cancer drugs

- Chronotherapy consists of coordinating the timing of a medical treatment with patient's biological rhythms in order to optimise a drug's beneficial effects and reduce the undesired ones
- Tolerability varies in mice and rats by as much as 10-fold for >35 anticancer drugs (e.g. Oxaliplatin, 5-FU, Docetaxel,..) [1] ;2000 patients in Phase I, II & III trials
- Oxaliplatin was "rescued" using adjusted chronotherapeutic regimes [1]
- Phase III: Oxaliplatin-5FU combination chronotherapy with gender effect (2-Year survival male increase by 25%, but female decrease by 38%) [2]
- Much evidence for circadian regulation of the cell cycle in a variety of cell types [3] and this synchronisation may be lost in tumours [4].

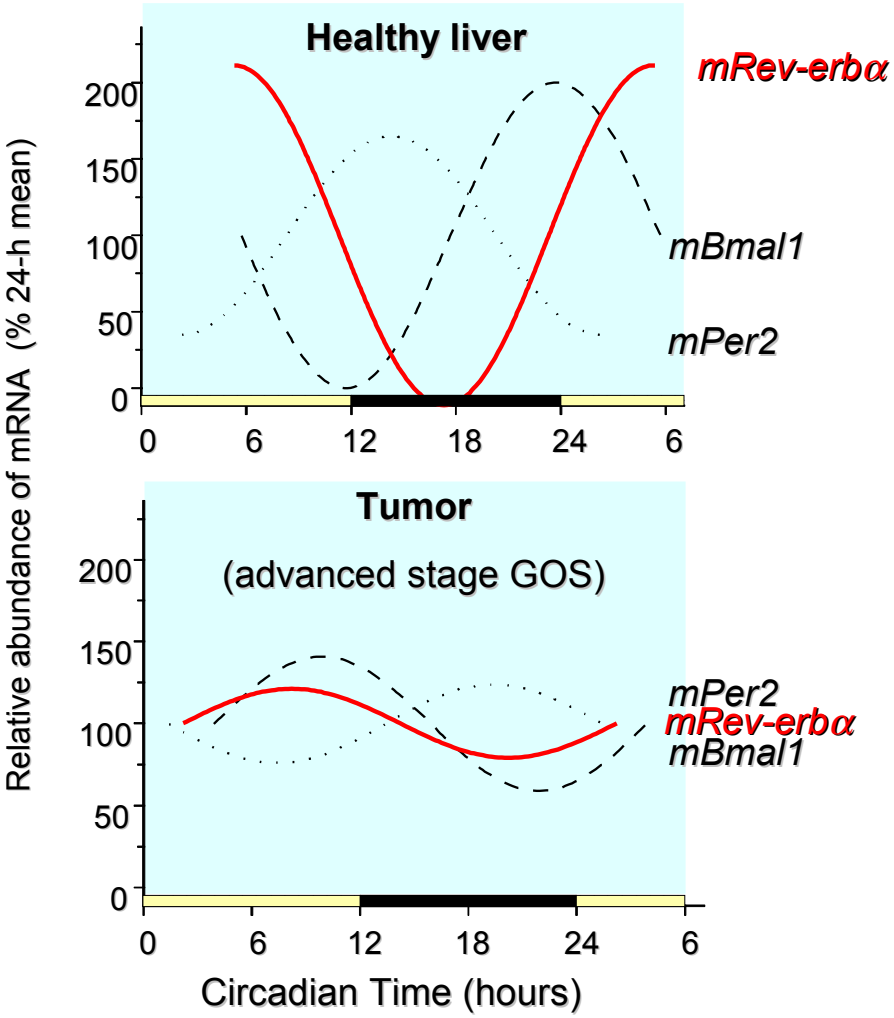
[1] Levi F. & Schibler U., Ann Rev Pharm Tox (2007); 47:593-528
[2] Giacchetti et al. J Clin Oncol 2006, 24:3562-3569
[3] Levi F., IEEE Eng Med Biol Mag. (2008); 27(1):17-9.
[4] Iurisci I. et al., Cancer Res (2006); 10720-8.

Circadian rhythms



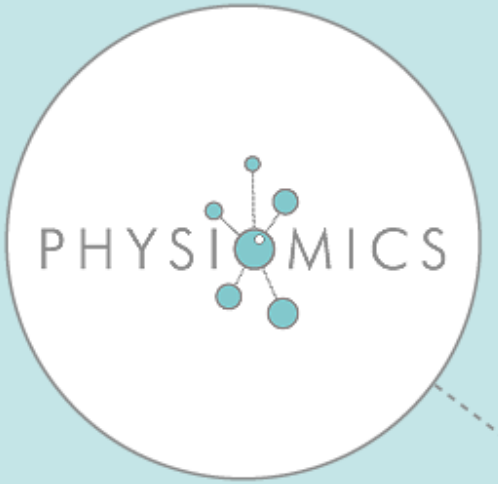
Source: http://en.wikipedia.org/wiki/Image:Biological_clock_human.PNG

Altered molecular clock in experimental tumors



- **Dividing cells: targets for cancer therapeutics**
- **(no specificity for cancer cells)**
- **Cell cycle**
  - deregulated in cancer cells
  - controlled by circadian timing system in normal cells

Iurisci I. et al., Cancer Res (2006); 10720-8.

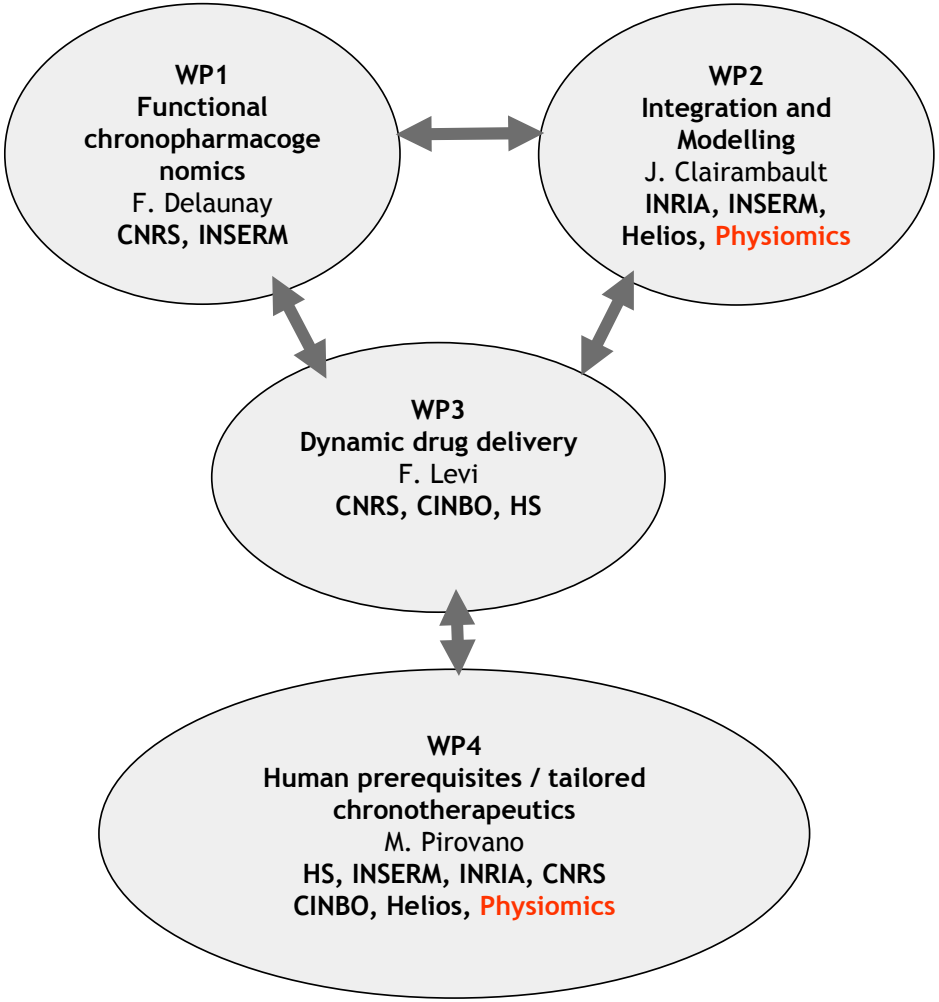


TEMPO project

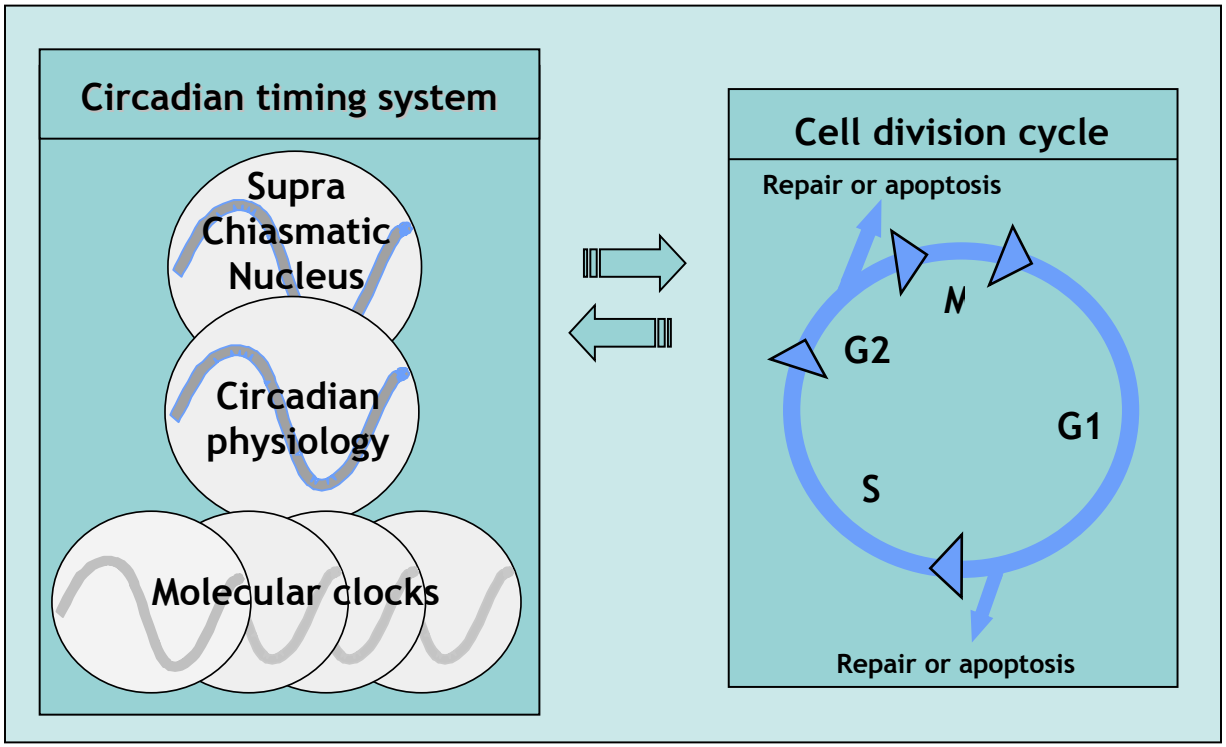
This research is supported by European Commission FP6
Specific Targeted Project
TEMPO LSHG-CT-2006-037543

Tempo (EU project , 8 partners) General Objectives

- **Design 3 to 5 chronotherapeutic schedules based on patient profiling, identified by:**
  - Set of 20 to 30 marker genes
  - Cell cycle, drug activity & pattern tolerability & efficacy
  - Addressing gene expression , proteins, signaling pathways, biochemistry
  - Mathematical models
- **Application: patient-tailored cancer chronotherapeutics:**
  - Seliciclib
  - Irinotecan
- **Validation during the project:**
  - Optimal schedules in cell cultures, animal models and development of micro-pumps for drug delivery
  - Human prerequisites and theoretical schedules

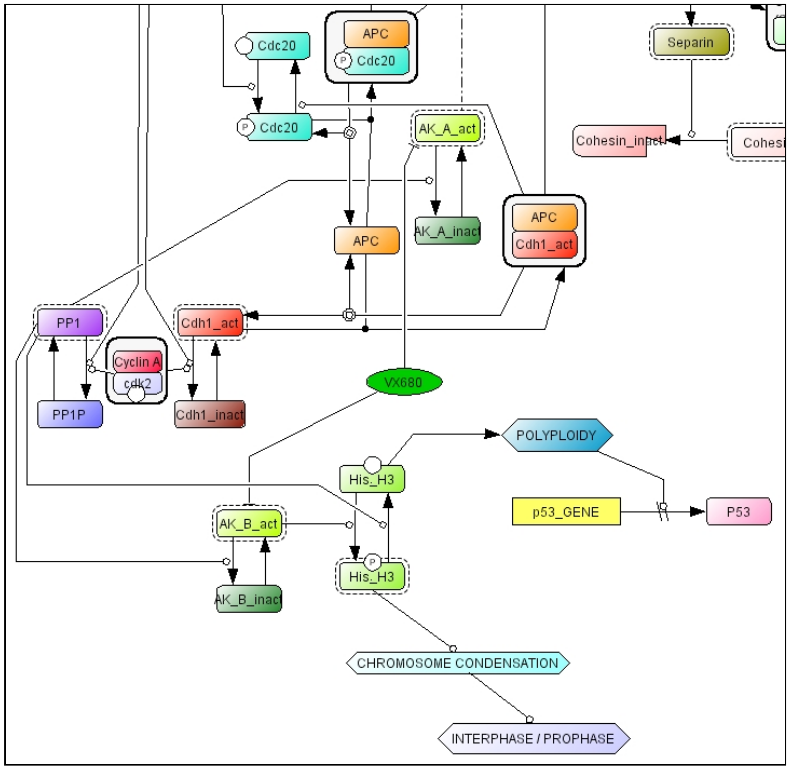


TEMPO (EU project)
Chronotherapy Modelling

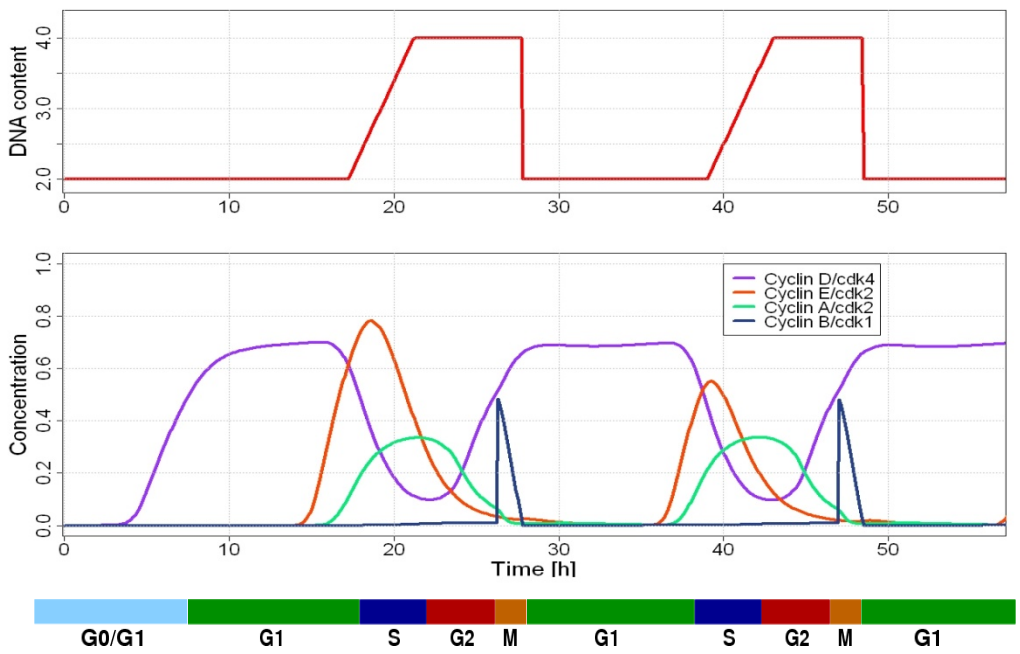


Therapeutic implications of the interactions between the circadian timing system, the cell division cycle and the pharmacology determinants

Snapshot of the Mammalian Cell Cycle Model

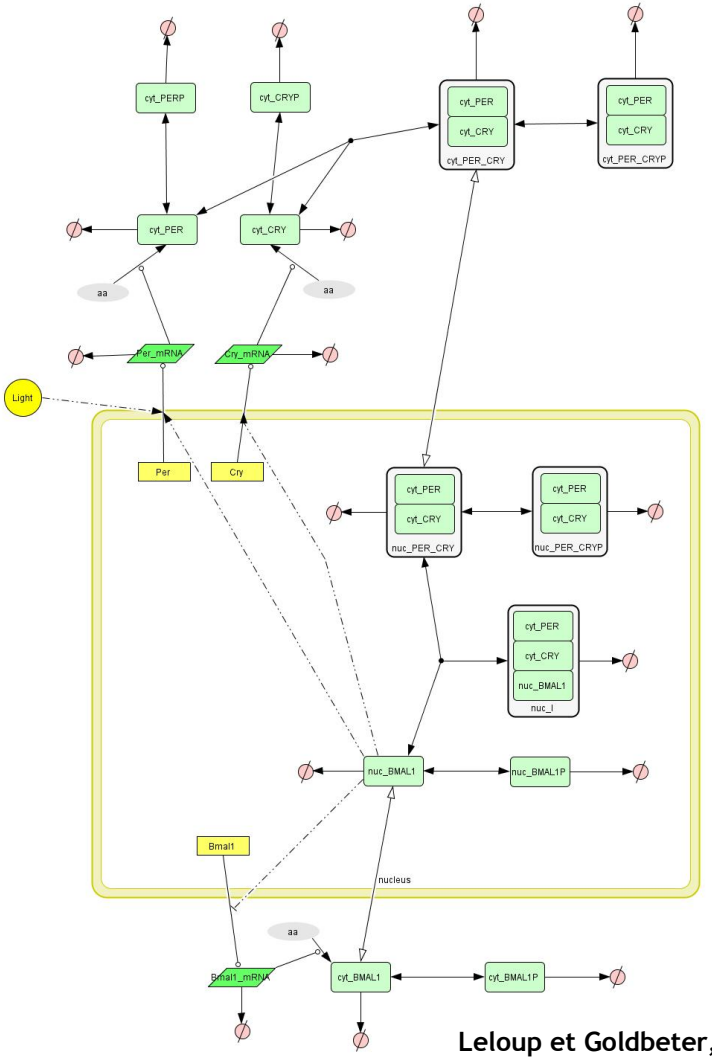


The diagram shows cell cycle phases & components within a fragment of the mitosis module.



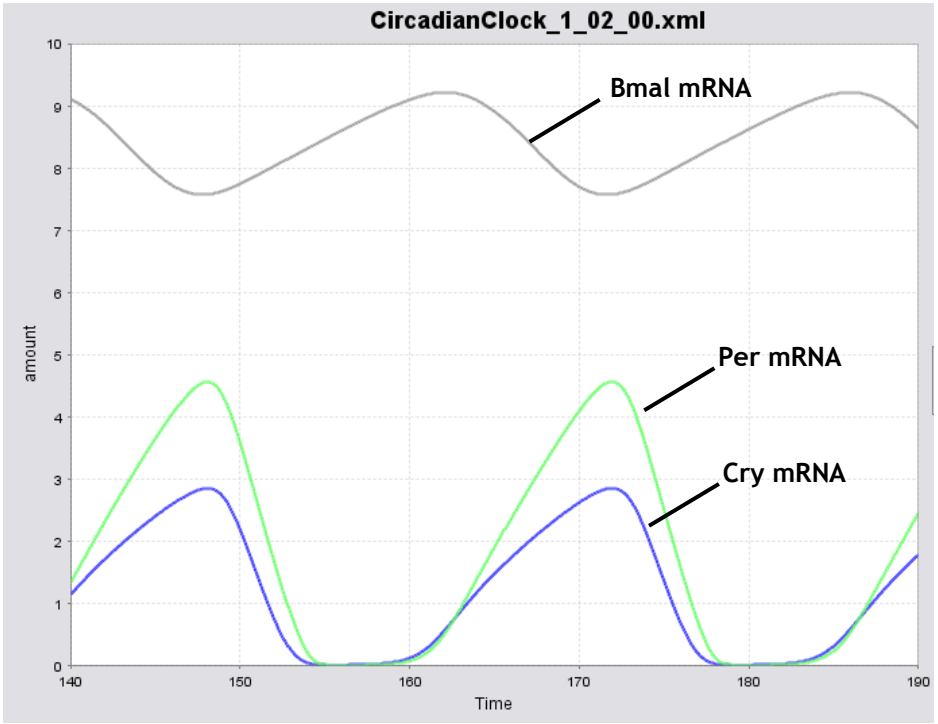
Two wild-type mammalian cell cycles starting from G0 arrest: DNA replication (top) and time courses of cyclins E, D, A & B in complex with cdks (bottom) are shown.

Circadian Clock Model (molecular clock)

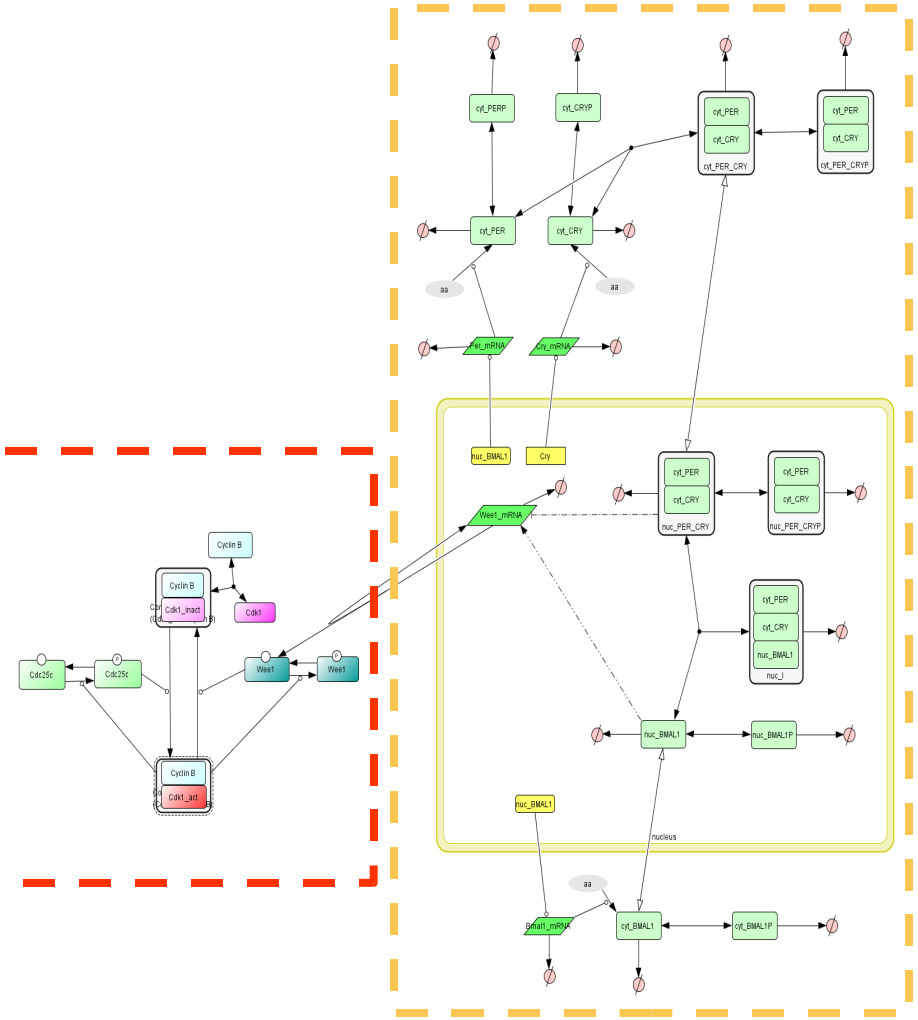


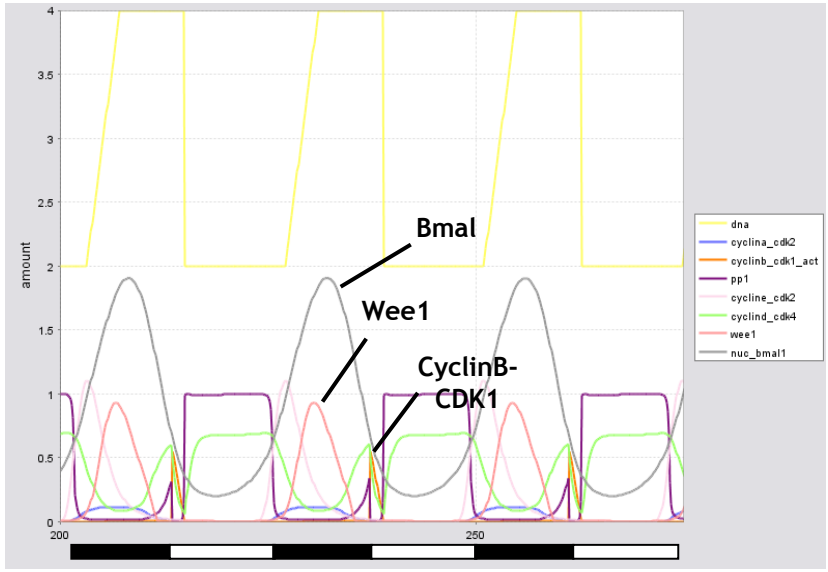
Leloup et Goldbeter, PNAS 2003

"16 equations model"



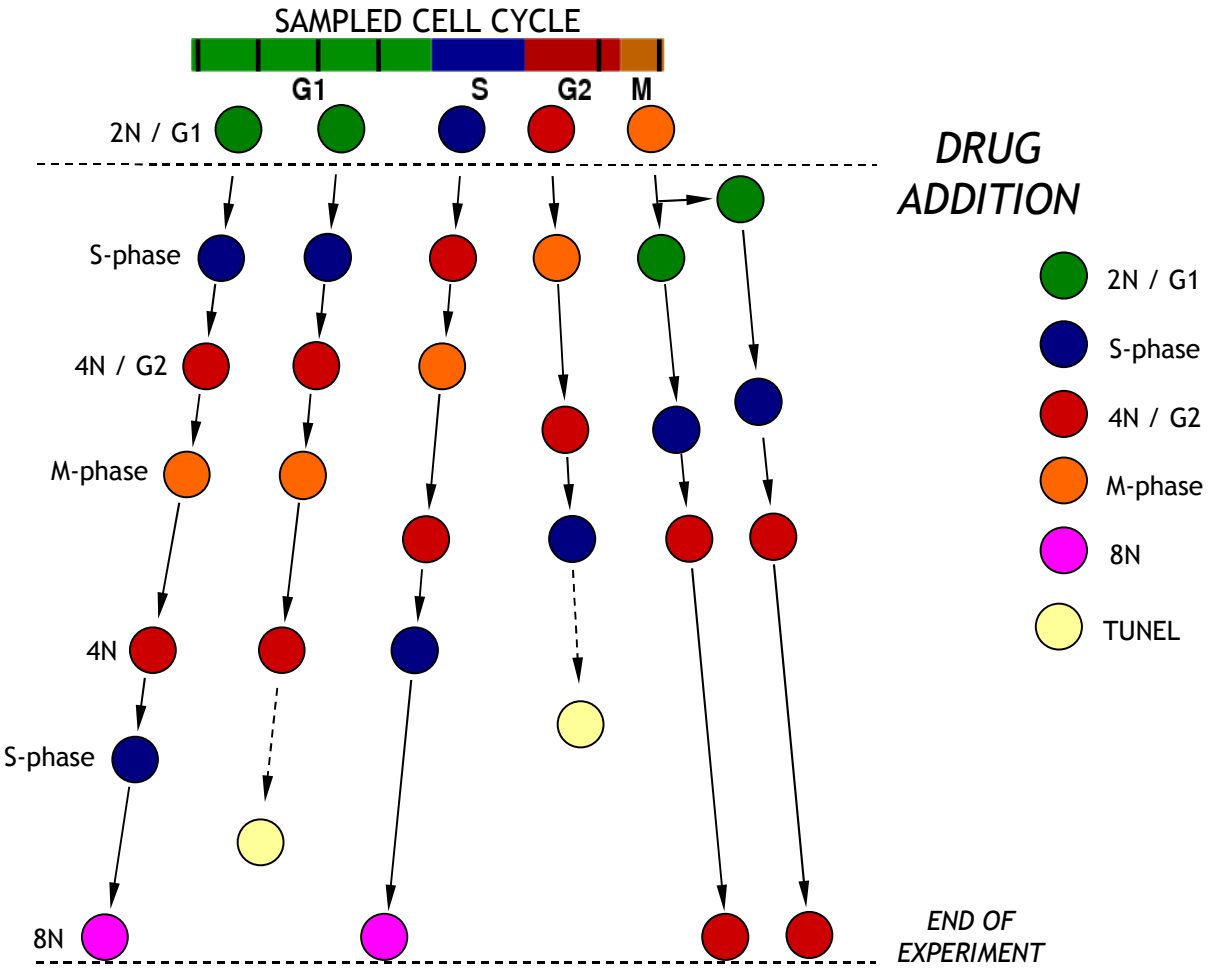
Coupled Cell Cycle - Circadian Clock model



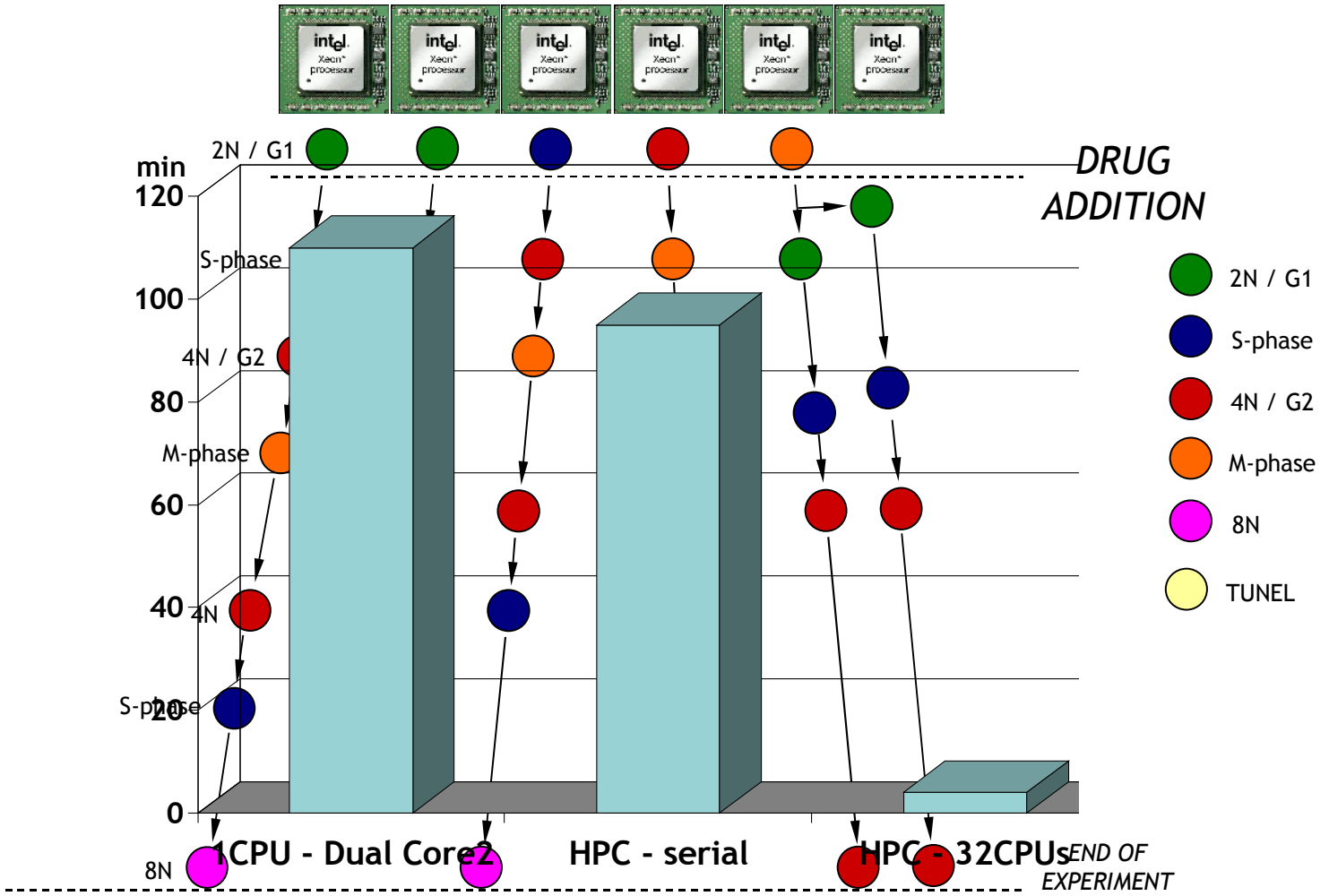


Left: the circadian clock model (dotted orange rectangle) was coupled to the cell cycle model through the CyclinB-cdk1 mitotic switch (red dotted square) via its regulator Wee1. **Top:** Simulation showing the entrainment of some cell cycle species by the circadian clock.

Virtual FACS - SystemCell® Technology

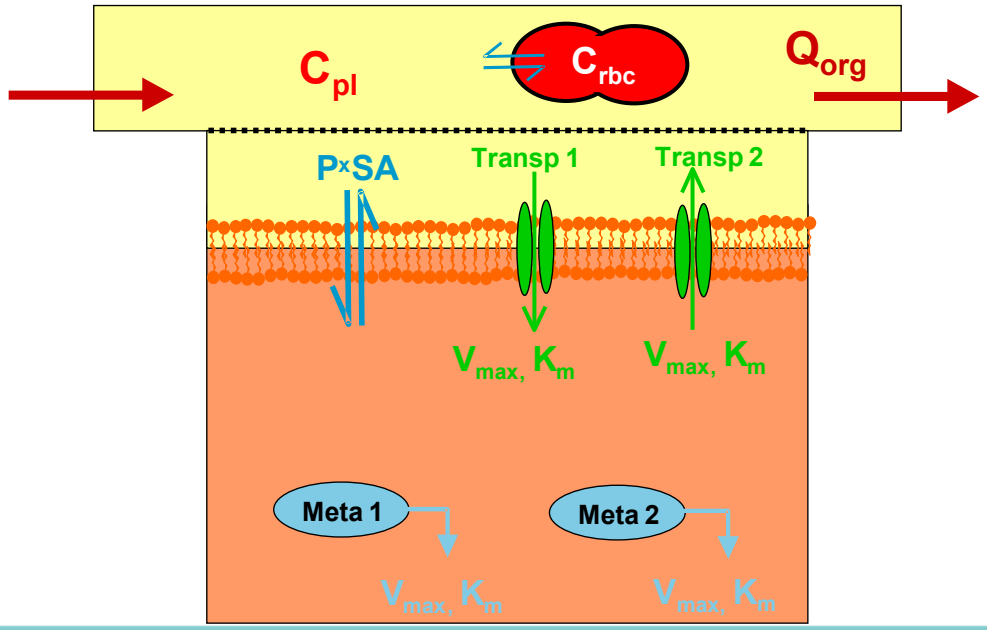


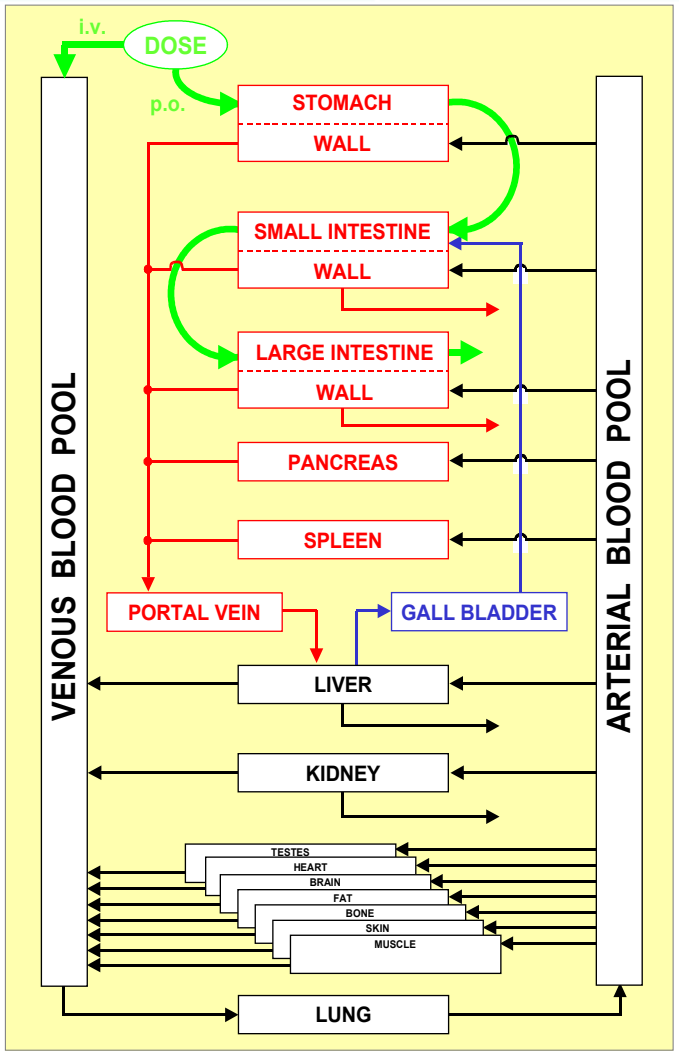
HPC - SystemCell® Technology



PK Modelling Approach

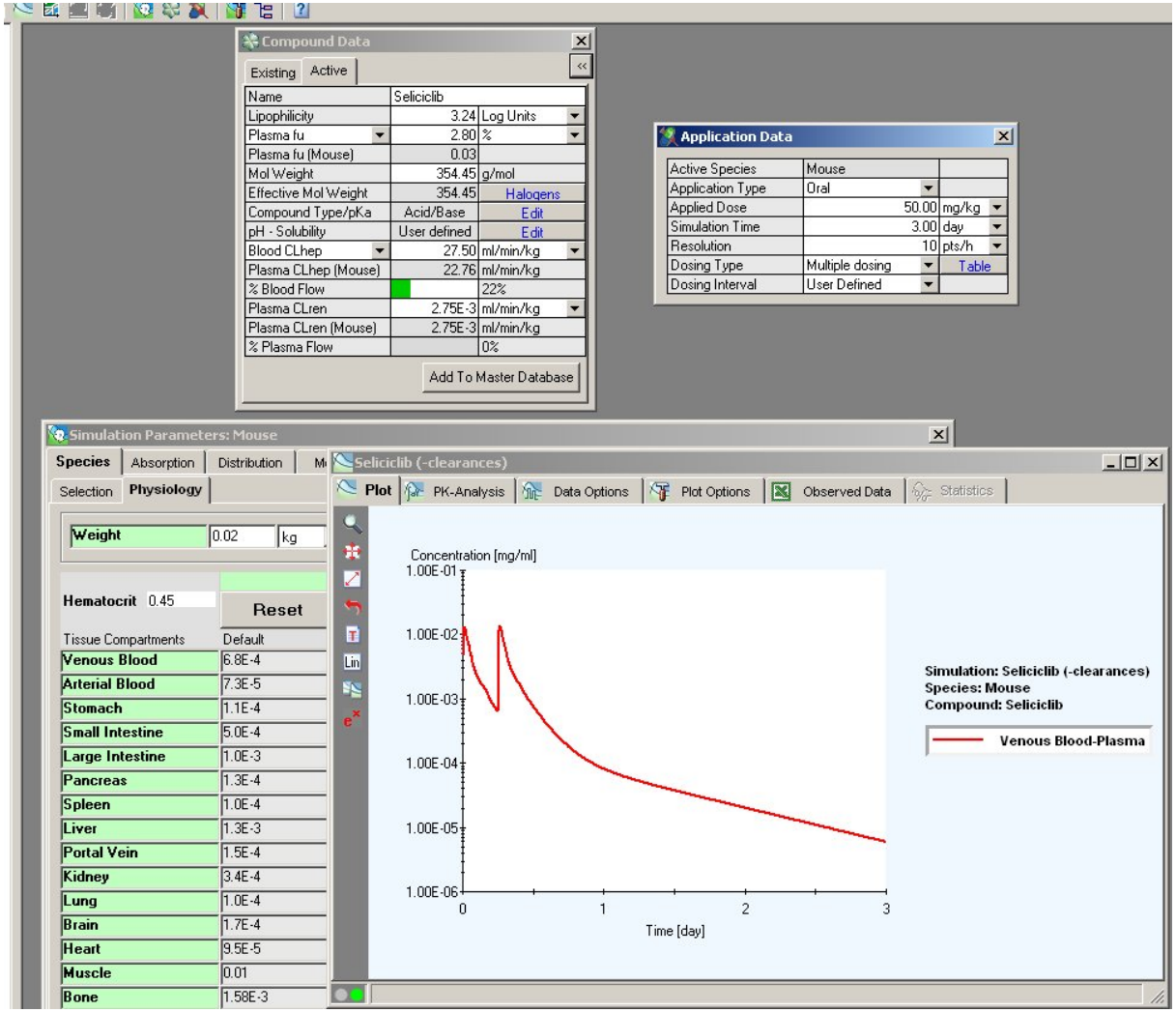
- Chosen to use a mechanistic (PBPK) model provided by PK-Sim™:
  - The model is preconstructed to include compartments for different tissues (useful for simulations of toxicity)
  - Extrapolation from mouse to human is based on physiological mechanisms so may be more accurate.



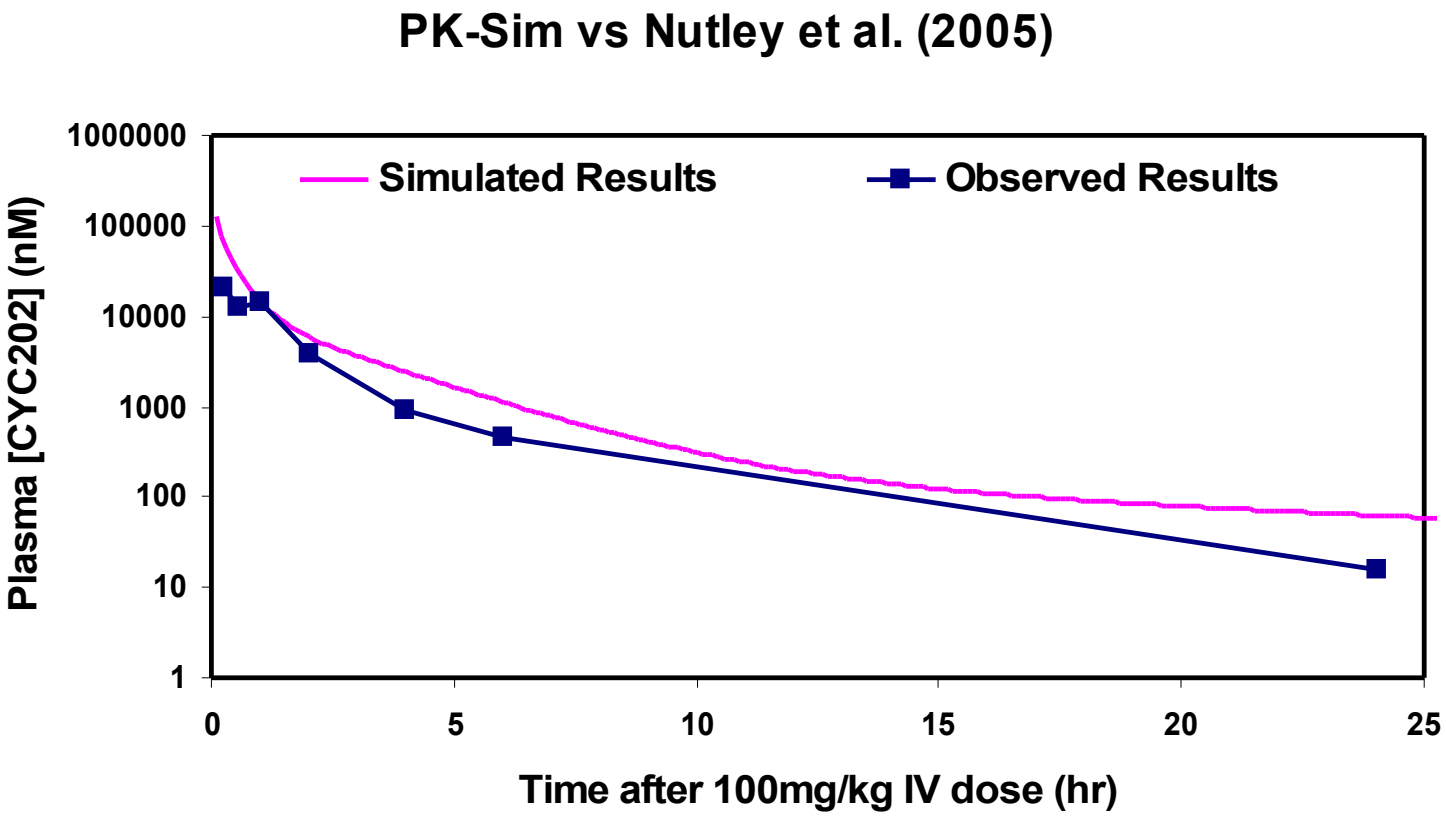


Pharmacokinetic Modelling – First Sketch

- We are currently using literature-derived and experimentally determined values for physicochemical properties of roscovitine
- No calibration has been performed for distribution (active transport) and organ-specific metabolism (actually experimentally determined)
- Therefore, only the plasma concentration-time courses are used as an input to the pharmacodynamic model



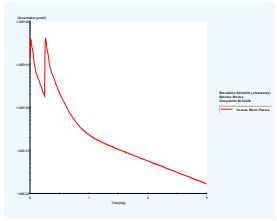
Pharmacokinetic Modelling



100mg/kg IV dose published by: Nutley et al.; Mol Cancer Ther 2—5;4(1), 125-139

Combined PK-PD Modelling

PK profile



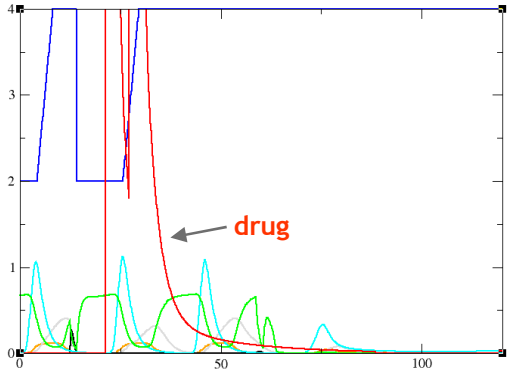
Conversion and rescaling

```
#time   uM
0       0
0.060526316     1.2
0.121052632     2.4
0.181578947     3.6
0.242105263     4.8
0.302631579     6
0.363157895     5.612872
0.423684211     5.237883
0.484210526     4.875008
0.544736842     4.524247
...
```

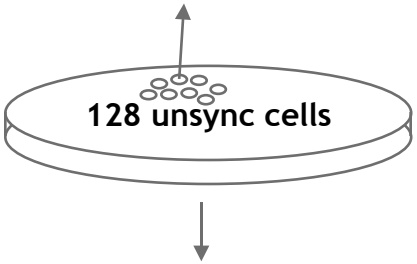
Dose scheduling

SystemCell® for HPC

Cell population

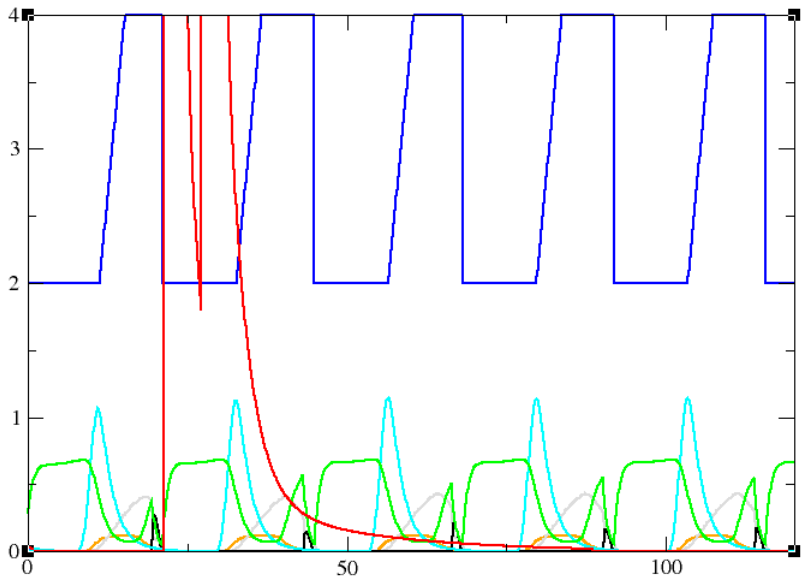


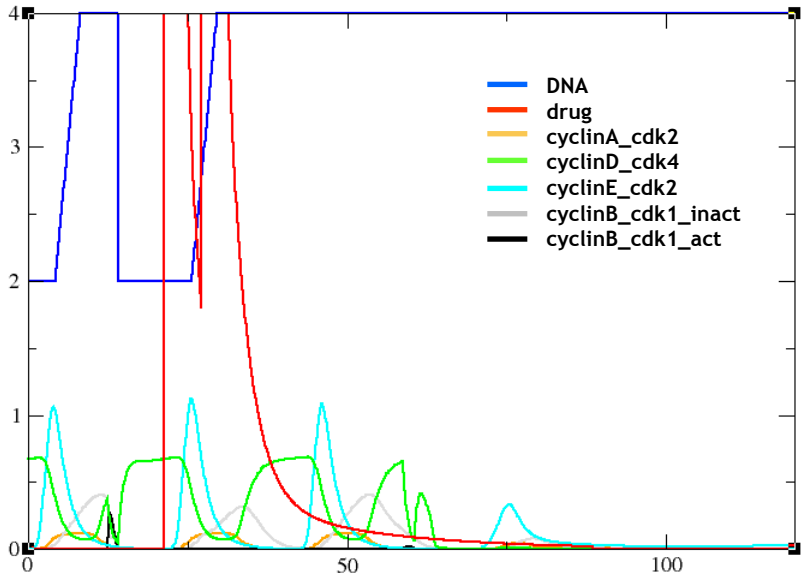
Example single cell



- DNA content (virtualFACS)
- pHH3 (IVTI)
- Mitotic index

Single Cell Combined PK-PD Modelling





- When administered at early G1 double Seliciclib dosing barely effects cell cycle length.

- When administered at late G1-G2, Seliciclib leads to sustained G2 arrest

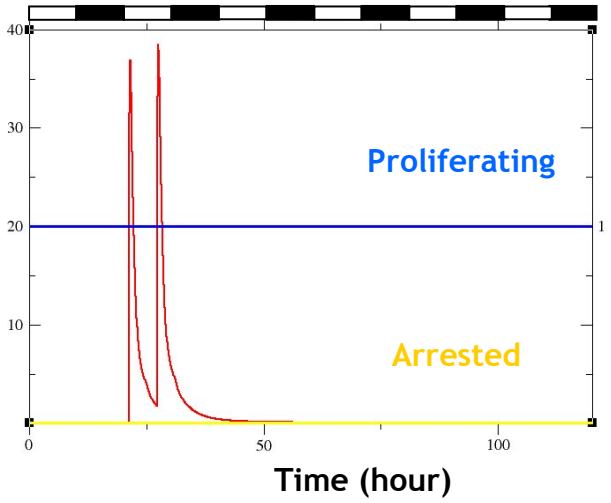
Fernandez, E. et al, Abstract No 801, AACR Annual Meeting 2008,San Diego, CA

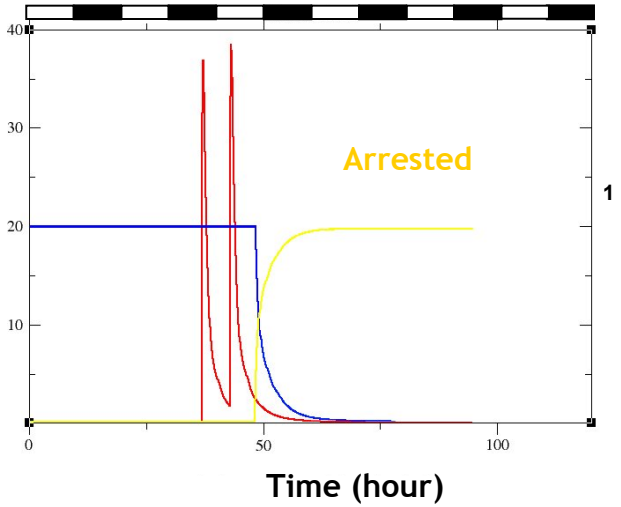
Multi-cell Combined PK-PD Modelling

Dose given at ZT3

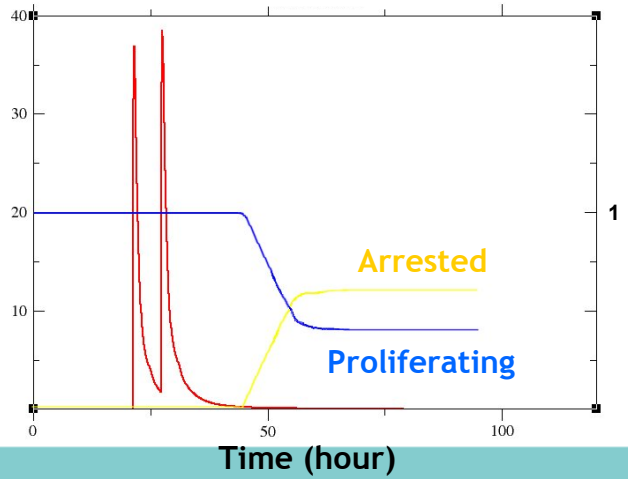
Dose given at ZT19

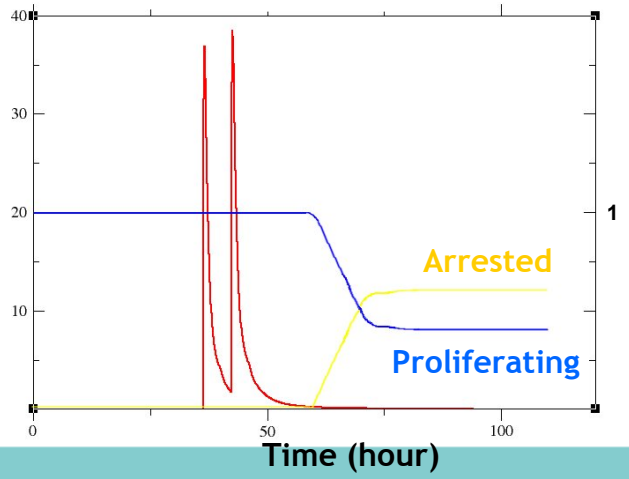
Synchronised cell population





Unsynchronised cell population





Experimental Data

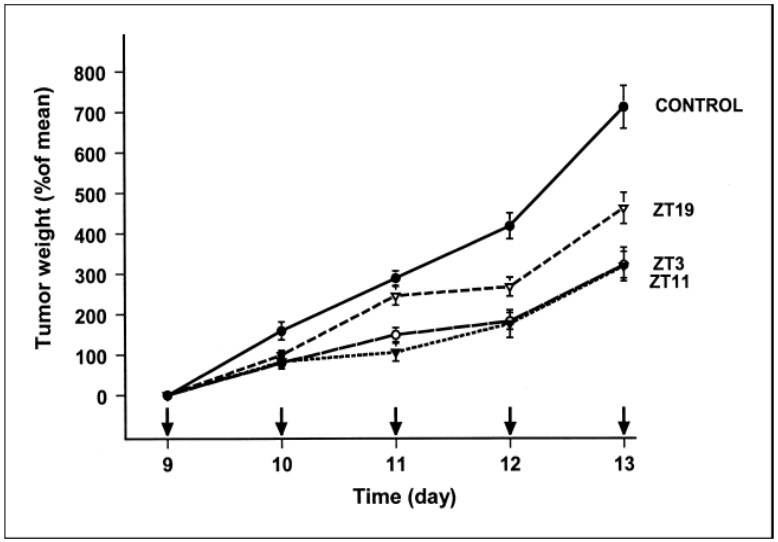


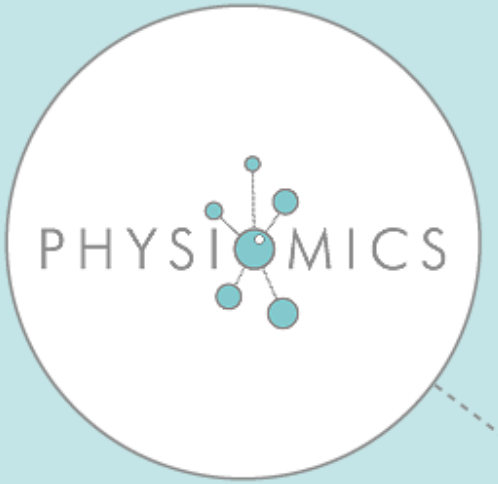
Figure 2. Dosing time-dependent effects of Seliciclib on tumor growth. Tumor weight change as a function of Seliciclib administration time. ●, controls; ○, treated at ZT3; ▲, treated at ZT11; Δ, treated at ZT19. Treatment started on day 9 after tumor inoculation. *Arrows*, days of drug injection. Thirty-six controls and 32 mice were allocated to each treatment group. *Points*, mean; *bars*, SE. Differences between controls and animals treated at ZT3, ZT11, or ZT19 were validated with ANOVA ($P < 0.001$).

. Seliciclib toxicity was the lowest following dosing at ZT3 (lethal toxicity rate, 3.1%) compared with ZT11 (6.2%) or ZT19 (21.9%; $P = 0.07$, Fisher's exact test).

- **Experimental data in mice (Iurisci et al. Cancer Res (2006) 10720-8) is broadly in line with our initial simulations.**

Perspectives – Future work

- Simulate effects of Seliciclib on apoptosis
- Add regulation of apoptosis by circadian clock (balance cell division/cell death)
- Models for each organ – calibrated with experimental data
- Adapting model for Human (clinical trial design)
- New dosing regimen and delivery protocols for cancer drugs



Thank You

cchassagnole@physiomics-plc.com

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